JPPT | Case Report

Therapeutic Drug Monitoring of Levofloxacin in an Obese Adolescent: A Case Report

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OBJECTIVES To describe the pharmacokinetics of levofloxacin in an obese adolescent patient in the pediatric intensive care unit.

METHODS A single-patient medical record review was conducted.

RESULTS A 168-kg, 15-year-old female with past medical history of Prader-Willi syndrome and asthma initially presented with respiratory distress secondary to asthma exacerbation. She failed non-invasive ventilation and was subsequently intubated for respiratory failure and progressed to high-frequency oscillatory ventilation. On hospital day 1 (HD 1) an infectious workup was begun because of a fever, worsening clinical status, and initiation of vasopressors and an empiric antimicrobial regimen of cefepime and clindamycin. The urine culture subsequently grew *Escherichia coli* and the respiratory culture grew *Pseudomonas aeruginosa*. She continued to be febrile, which was thought to be due to an intra-abdominal abscess. On HD 14, the antimicrobial regimen was changed to levofloxacin because of continued fevers and no significant clinical improvement. Levofloxacin was initiated at 1000 mg IV every 24 hours. Levofloxacin serum levels were obtained at 0.5, 3.5, and 11.5 hours after infusion, which were 8.61, 5.76, and 2.7 mg/L, respectively. These concentrations translated into a peak level of 8.79 mg/L, a half-life of 6.4 hours, and an AUC of 80 mg·hr/L, which are discordant from the expected peak of 16 mg/L, a half-life of 8 hours, and an AUC of 120 mg·hr/L. Based on these values, the levofloxacin regimen was adjusted to 1000 mg IV every 12 hours, and repeat levels 0.5, 3.5, and 11.5 hours after infusion were 9.91, 6.56, and 3.27 mg/L, respectively, corresponding to a peak of 10.5 mg/L, a half-life of 5.18 hours, and an AUC of 200 mg·hr/L. After the adjustment in levofloxacin regimen, she became afebrile, WBC resolution and improvement in her overall clinical status, and she received a total duration for levofloxacin of 21 days.

CONCLUSION A levofloxacin regimen of 1000 mg IV every 12 hours was successful in providing for an appropriate AUC exposure and was associated with a successful clinical outcome in this morbidly obese adolescent.

ABBREVIATIONS AUC, area under the concentration-time curve; CL, clearance; C_{max}, maximum concentrations; Ct, concentration at specified time; k_e, elimination rate constant; HD, hospital day; MIC, minimum inhibitory concentration; PICU, pediatric intensive care unit; $t_{1/2}$, half-life; Vd, volume of distribution; WBC, white blood cell

KEYWORDS adolescent; case report; levofloxacin; pharmacokinetic; pharmacodynamics; pediatric; obesity

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Introduction

The impact of obesity on the pharmacokinetic parameters of antibiotics and pediatrics in general is not well studied. Often clinicians will dose using total body weight or body surface area, which may result in subtherapeutic or supratherapeutic exposure. They might also extrapolate from adult data and dose based on ideal body weight, but this may result in underdosing and subsequent therapeutic failures, highlighting the need for therapeutic drug monitoring.[1–3] Obesity alters the normal physiology, which can affect the pharmacokinetics of drugs, including drug absorption, volume of distribution, metabolism, and elimination. Additionally, the lipophilicity or protein binding of the drug may further lead to alterations of drug pharmacokinetics on obese children.[4,5] Furthermore, critical illness also has been shown to lead to alterations in pharmacokinetic parameters.[4,6–8] Therefore, an understanding of the pharmacokinetic changes in critically ill obese children in the PICU is imperative to determining an optimal antimicrobial regimen.[9]

Levofloxacin, a broad-spectrum fluoroquinolone, is not commonly used in the PICU, and little is known about dosing of levofloxacin in obesity. Levofloxacin is used for both hospital- and community-acquired infections. In children age ≥5 years, the dose is 10 mg/kg per dose once daily, with a maximum of 750 mg once daily.[10] The pharmacokinetic parameters of levo-

floxacin in pediatric patients demonstrate absorption and distribution similar to those in adults.[11] However, levofloxacin elimination has been described as age dependent, with children younger than 5 years clearing levofloxacin twice as fast as adults, resulting in lower AUC.[12] The available pharmacokinetic data for levofloxacin in obese patients are limited to adults only and demonstrated peak concentrations similar to those in non-obese individuals but variable clearance and AUC values.[11,13] To date, there have been no pharmacokinetic studies evaluating levofloxacin in an obese pediatric patient. The purpose of this case report is to describe the pharmacokinetics of levofloxacin in an obese adolescent patient in the PICU. This was a retrospective chart review of a single patient's medical record.

Case

A 15-year-old female with Prader-Willi syndrome, asthma, and obesity (weight, 168 kg; height, 153 cm; body mass index, 71.8 kg/m^2) initially presented with respiratory distress secondary to an asthma exacerbation. Initially the patient was started on non-invasive ventilation, which she failed, and was subsequently intubated for respiratory failure that progressed, requiring high-frequency oscillatory ventilation. On hospital day 11 (HD 11) an infectious workup was started because of fever, worsening clinical status, and initiation of vasopressors, and cefepime and clindamycin were empirically started. A urine culture subsequently grew *Escherichia coli* and a respiratory culture grew *Pseudomonas aeruginosa*. The susceptibilities are listed in Table 1. Despite adequate antibiotics the patient continued to be febrile, which was thought to be due to an intra-abdominal abscess. On HD 14, the antibiotic regimen was changed to levofloxacin because of continued fevers and no significant improvement in clinical status. At that time the patient's serum creatinine was 0.85 mg/dL, cystatin C was 1.15 mg/L, and estimated glomerular filtration rate was 74.2 mL/min/1.73 m^2. Levofloxacin was initiated at a dose of 1000 mg IV every 24 hours infused during 60 minutes. Serum concentrations were obtained 0.5, 3.5, and 11.5 hours after infusion following the first dose and were 8.61, 5.76, and 2.7 mg/L, respectively (Table 2).

Table 1. Organism Isolates and MICs

Date	Source	Organism	Drug	MIC, mg/L
HD 3	Urine	EC	AMK	≤2
			SAM	≤2
			AMP	≤2
			ATM	≤1
			CFZ	≤4
			FEP	≤1
			CTX	≤1
			CAZ	≤1
			CIP	≤0.25
			DOR	≤0.12
			GEN	≤1
			MEM	≤0.25
			NIT	≤16
			TZP	≤4
			TOB	≤1
			SXT	≤20
HD 3	ASP	PA	AMK	≤2
			FEP	≤1
			CAZ	2
			CIP	≤1
			GEN	≤1
			MEM	≤0.25
			TZP	8
			TOB	≤1

AMK, amikacin; AMP, ampicillin; ASP, endotracheal tube aspirate; ATM, aztreonam; CAZ, ceftazidime; CFZ, cefazolin; CIP, ciprofloxacin; CTX, cefotaxime; DOR, doripenem; EC, Escherichia coli*; FEP, cefepime; GEN, gentamicin; HD, hospital day; MEM, meropenem; NIT, nitrofurantoin; PA,* Pseudomonas aeruginosa*; SAM, ampicillin/sulbactam; SXT, trimethoprim-sulfamethoxazole; TOB, tobramycin; TZP, piperacillin-tazobactam*

Concentrations for levofloxacin in plasma were determined by high-performance liquid chromatography at the National Jewish Health Advanced Diagnostics Laboratory (Denver, CO). A non-compartmental pharmacokinetic analysis was conducted to determine the elimination rate constant (k_e), half-life ($t_{1/2}$), and volume of distribution (Vd), and to calculate the AUC. The following equations were used in determining patient-specific pharmacokinetic variables:

Dose (mg) = Co (mg/L) × Vd (L);

Ct = Co (mg/L) × e-kt; and

AUC = dose (mg)/L, where CL = k_e (hr^{-1}) × Vd (L/kg),

where Ct = concentration at specified time; Co = initial concentration; and CL = clearance, and $t_{1/2}$ = ln(2)/k, where k is the elimination rate constant.

The levofloxacin serum concentrations of 8.61, 5.76, and 2.7 mg/L corresponded to a peak level (Ct) of 8.79 mg/L, a half-life of 6.4 hours, and an AUC of 80 mg/L·hr, which are discordant from the expected values detailed in the package insert of a peak level of 16 mg/L, a half-life of 8 hours, and an AUC of 120 mg/L·hr (Table 3).[11] On day 11 of levofloxacin therapy and day 14 of antibiotics, levofloxacin dosing was adjusted to 1000 mg IV every 12 hours. Repeat levofloxacin serum concentrations were obtained 0.5, 3.5, and 11.5 hours after infusion on day 4 of the adjusted levofloxacin regimen and were 9.91, 6.56, and 3.27 mg/L, respectively (Table 2). These levels corresponded to a peak (Ct) of 10.5 mg/L, a half-life of 5.18 hours, and an AUC of 200 mg/L·hr (Table 3). The patient did not receive any medications that are

Table 2. Levofloxacin Serum Concentrations

Time After Infusion, hr	Serum Concentration, mg/L	
	Dose of 1000 mg every 24 hr	Dose of 1000 mg every 12 hr
0.5	8.61	9.91
3.5	5.76	6.56
11.5	2.7	3.27

known to alter the pharmacokinetics of levofloxacin, and during therapy renal function was stable and glucose levels were normal, ranging between 96 and 140 mg/dL. After the adjustment in levofloxacin dosing, the patient became afebrile, with normalization in WBC count and overall clinical improvement. The patient was febrile with temperatures of at least 38.5°C for 7 days prior to changing to levofloxacin. Although the patient remained febrile with the levofloxacin on an every-24-hour dosing regimen, the overall fever trend was down. Within 24 hours of changing to the every-12-hour levofloxacin regimen, the patient because afebrile and remained afebrile for the duration of levofloxacin therapy. The WBC count ranged from 18 × 10^3 to 25.7 × 10^3 cells/mcL prior to adding levofloxacin. Within 24 hours of initiating levofloxacin, the WBC count fell to 10 × 10^3 cells/mcL and remained in the range of 8 × 10^3 to 12.3 × 10^3 cells/mcL for the duration of levofloxacin therapy. The patient received levofloxacin for a total duration of 21 days.

Discussion

There are few studies describing levofloxacin dosing in obese patients, and to date there are no data describing levofloxacin dosing in stable or critically ill obese pediatric patients. Levofloxacin is considered a concentration-dependent antibiotic best represented by the ratios of maximum concentration (C_{max}) to MIC and AUC to MIC.[11] A target AUC/MIC greater than 87 mg/L·hr has been shown to result in greater probabilities of clinical and microbiologic cure and is an important pharmacodynamic target when treating Gram-negative infections.[14,15] Furthermore, an AUC/MIC of >100 mg/L·hr correlated with lower rates of treatment-emergent resistance.[14,15] Regardless of whether an MIC is obtained for an organism, when conducting pharmacodynamic MIC-based adjustments to dosing regimens, use of the epidemiologic cutoff value is suggested because the inherent limitations with MIC determination.[16] Therefore, clinicians need to remain cognizant when evaluating AUC values, such as those reported in the package insert, and AUC/MIC values, such as those reported in the literature. In this case, the estimated AUC was 200 mg/L·hr, and using the epidemiologic cutoff value of 2 mg/L for levofloxacin against *P aeruginosa*, the AUC/MIC ratio is 100 mg/L·hr. Measuring drug concentrations of antibiotics and altering the dose based on serum concentrations and pharmacodynamic parameters have been found to result in improved outcomes.[6,17] In patients with nosocomial pneumonia, dose alteration of fluoroquinolones, aminoglycosides, or β-lactam antibiotics based on pharmacodynamic indices resulted in improved microbiologic clearance and clinical outcomes compared with using standard recommended dosing without dose alteration.[17] With once-daily dosing, we were unable to achieve an adequate AUC and AUC/MIC ratio, but when changed to every-12-hour dosing, our patient's levofloxacin AUC was 200 mg/L·hr, and the AUC/MIC ratio was 100 mg/L·hr, and this correlated to clinical improvement. Our patient tolerated 1000 mg IV every 12 hours with no treatment-emergent adverse effects despite the fact that the highest dose of levofloxacin reported to be given is 1000 mg IV every 24 hours for patients with *Mycobacterium tuberculosis*.[18]

Levofloxacin has an extensive volume of distribution, with penetration into most tissues and body fluid, and it is primarily renally eliminated.[15] In adults, obesity has been found to alter levofloxacin pharmacokinetics, resulting in variable AUC.[13,19] Therefore, it is also likely that obesity alters the pharmacokinetic of levofloxacin in pediatrics.[11] The pharmacokinetics of a 750-mg dose of IV levofloxacin has been studied in obese adult patients.[13] Twelve hospitalized patients and 3 ambulatory care patients were included in 2 different cohorts, and results were compared to a previous pharmacokinetic study in healthy, non-obese adult volunteers. Serum samples were taken after the first dose of levofloxacin. This study found that peak plasma concentrations of levofloxacin in hospitalized and ambulatory patients were similar, being 8.4 and 7.84 mg/L, respectively, which was similar to the peak concentration found in healthy adult individuals of 8.2 mg/L. However, clearance and AUC were altered in obese patients compared with non-obese patients. In hospitalized obese patients, clearance was 139.7 ± 70.4 mL/min compared with 186 ± 5 mL/min in healthy non-obese adults, correlating to a mean AUC of 90.12 ± 40.8 mg/L·hr in hospitalized obese patients compared with 61.1 mg/L·hr in healthy volunteers.[13] Levofloxacin pharmacokinetics has further been described in a case report of a single morbidly obese adult patient with community-acquired pneumonia.[19] The patient was given levofloxacin 750 mg IV every 12 hours, and on day 3 of therapy the peak plasma concentration was 8.68 mg/L, and half-life was 16.15 hours, with a clearance of 174.5 mL/min, correlating to

Table 3. Levofloxacin Pharmacokinetic Parameters

	Package Insert, 750 mg IV	Patient, 1000 mg every 24 hr	Patient, 1000 mg every 12 hr
Co, mg/L	12	8.79	10.5
Half-life, hr	8	6.4	5.18
AUC, mg/L·hr	120–160	80	200

Co, initial concentration

an AUC_{0-24} of 143.27 mg/L·hr.[19] The pharmacokinetics of levofloxacin in our patient more closely resembles the single case report in a morbidly obese patient given the similar AUC.[19] The half-life in our patient was probably shorter given the patient's age and renal function.

Conclusion

The observed levofloxacin pharmacokinetics in our patient was different from what was reported in the package insert. Obesity had an effect on the levofloxacin pharmacokinetics, requiring a dose that was twice the highest dose reported to be given resulting in appropriate serum concentrations. This case report further emphasizes the need for therapeutic drug monitoring of antibiotics in critically ill obese patients.

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